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Laurence J Hyman
Townsend & Townsend & Crew
8th Floor
Two Embarcadero Center
San Francisco, CA 94111-3834

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,539	PASTAN ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *41-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 1-50 are pending.

2. Applicant's election with traverse of Group I, claims 1-26 and 33-40, in Paper No. 7 (9/3/2003) is acknowledged. The traversal is on the grounds that Groups I and II ashare the same technical feature. This is found persuasive because Groups I and II share the same technical feature and have been rejoined for examination in the instant application. The restriction between Groups III and IV is proper for reasons of record. For these reasons the restriction requirement is deemed to be proper and is made FINAL.

3. Claims 41-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 7 (9/3/2003).

4. Claims 1-40 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

a) This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

b) The first line of the specification should be updated with a priority statement, claiming benefit to U.S. provisional 60/160,071 filed 05/27/1999.

c) Page 12, line 8 should be updated to indicate that U.S. application 08/776,271 is now a U.S. Patent and indicate the patent number. The patent number is 6,083,502.

d) The disclosure is objected to because it contains an embedded hyperlink on page 20, line 13. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicants regard as their invention.

a) Claim 21 is indefinite for "comprising a surface protein of a bacteriophage". Is the polypeptide of claim 1 expressed by bacteriophage or not and does the protein further comprise just any surface protein of a bacteriophage?

b) Claims 1, 27 and 33 and those claims that depend from claims 1, 27 and 33 are indefinite for reciting "substitution of at least one amino acid .....selected from

AGY or RGYW". Are the nucleotide hot spot motifs (AGY or RGYW) part of the parental antibody sequence or are the nucleotide hot spot motifs (AGY or RGYW) part of the substituted/mutated sequence?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6 and 22 and those claims that depend from claims 6 and 22 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody SS is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the

chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species antibody SS.

The specification lacks complete deposit information for the deposit of anti-mesothelin antibody SS. It is unclear whether antibodies possessing the identical properties of antibody SS are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody SS, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record

who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of antibody SS has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of antibody SS is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The specification provides sufficient guidance teaching one of ordinary skill in the art how to make the mutant antibodies SS1, D8, C10 and E4 provided that antibody SS is publicly available (see examples 1 and 8, Figure 3, and pages 22-25). Therefore, a deposit requirement is not made for mutant antibodies SS1, D8, C10 and E4.

10. Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies or nucleic acids that encode antibodies

comprising both VH and VL domains wherein the antibody binds the same antigen as the parent and compositions comprising such and methods of treatment with such antibodies, does not reasonably provide enablement for antibodies that only have a VH or a VL chain alone and do not bind antigen or binds antigens different from the parent as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

a) The claims are broadly drawn to antibodies, nucleic acids encoding said antibodies and methods of using said antibodies that only contain a mutated VH or a mutated VL chain and bind antigen or don't bind antigen as that of the parent antibody.

The specification discloses only antibodies that contain both a VH and a VL chain and the antibodies bind antigen and antibodies with increased affinity that bind the same antigen as the parent antibody (see examples). The specification does not enable antibodies, which only have a mutated VH or a mutated VL chain and bind antigen for treatment of malignant cells.

Claims 33-40 encompass malignant cell (i.e. tumor) treatment methods using antibodies that only have a mutated VH or a mutated VL chain and bind antigen. The specification does not enable antibodies, which only have a mutated VH or a mutated VL chain and bind antigen.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies that only have a VH or a VL chain as defined by the claims, which would contain less than the full complement of CDRs from the heavy and light chain variable

regions of an antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies that only have a VH or a VL chain and bind antigen as broadly defined by the claims. Thus, one of skill in the art would not know how to use antibodies that do not bind antigen and undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would indeed be required to perform undue experimentation in order to practice the claimed invention.

b) With respect to claim 21, claim 21 is broadly drawn to expressing mutated antibody polypeptides comprising a surface protein of a bacteriophage. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted to mean bacteriophage expression (i.e. phage display) of the mutated antibody polypeptides of claim 1.

The specification teaches expression of scFVs wherein the scFvs are expressed as fusions to the gIII protein (gIIIp) expressed on the surface of filamentous phage.

The specification does not teach expression of scFVs wherein the scFvs are expressed as fusions to any phage surface protein other than the gIIIp phage surface protein.

No specific direction or guidance is provided to assist one skilled in the art in the expression of mutated antibody polypeptides as fusions to any surface protein other than the gIIIp, nor is there evidence provided that antibody fusions to just any phage

surface protein will result in the selection of a high affinity antibody that binds antigen and would have therapeutic utility for treating malignant cells.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would indeed be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-5, 8, 10, 21, 27 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Yelton et al (The Journal of Immunology. 155: 1994-2004, 1995).

The claims recite a mutated antibody having at least 5 times higher binding affinity for an antigen compared to the parental antibody and the antibody has at least one amino acid substitution in a CDR wherein the amino acid is encoded by a codon comprising a nucleotide sequence selected from AGY or RGYW and the antibody is a

scFv, a Fab, or a F(ab)2. Claims 27 and 31 recite nucleic acids encoding the mutated antibody of claim 1 and an expression cassette, respectively. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted as being drawn to the bacteriophage expression (i.e. phage display) of the mutated antibodies. Due to the indefinite nature of the claims (see 112 2nd (b) on pages 3-4 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the substituted/mutated sequence (i.e. A/CNN or NNG/T).

Yelton et al teach affinity maturation of a monoclonal antibody (BR96) wherein several mutants (M1, M3 and M4) showed at least five-fold increased affinity (see abstract and Figures 4, 6 and 7). Yelton et al teach that the BR96 antibody is a Fab or scFv (see page 1997, left column) and comprises a bacteriophage surface protein. Yelton et al teach nucleic acids and expression cassettes encoding the mutated antibodies (see page 1995). Further, Yelton et al teach codon-based mutagenesis which efficiently introduces large numbers, and potentially all combinations of amino acid substitutions into a specifically targeted CDR (see page 1995, left column). Yelton et al teach that codon-baed mutagenesis of each of the CDRs of the BR96 heavy chain yielded mutants with increased affinity for tumor antigen (see page 1995). Yelton et al teach codon-based oligonucleotides, which include A/CNN (see page 1996) and NNG/T (see page 1997), where N is any nucleotide and NNG/T yields 32 codons, representing all twenty amino acids. Therefore Yelton et al anticipate the claims because codons AGY and RGYW are encompassed by the codons A/CNN and NNG/T.

13. Claims 1-5, 8, 10, 12-14, 16, 21, 27 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Marks et al (U.S. Patent 5,977,322, 102(e) date 6/13/1996).

The claims have been described supra. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted as being drawn to the bacteriophage expression (i.e. phage display) of the mutated antibodies. Due to the indefinite nature of the claims (see 112 2nd (b) on pages 3-4 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the substituted/mutated sequence.

Claims 12-14 and 16 further limits the mutated antibody of claim 1 by reciting that the antibody further comprises a label or therapeutic moiety such as *pseudomonas endotoxin* or a toxic moiety such as dipthera toxin, saporin, pokeweed antiviral toxin, ricin or bryodin.

Marks et al teach mutated antibodies expressed by phage display that specifically bind the extracellular domain of the c-erbB-2 protein product of the Her2/neu oncogene, wherein one or more of the variable light and heavy chain CDRs are mutated (see column 2) or randomized using NNS oligonucleotides (see column 21 and Table 18) and the affinity of the C6.5 (scFV specific for c-erbB-2) antibody was increased 5 fold by heavy chain shuffling and 6 fold by light chain shuffling (see column 17). Because NNS oligonucleotides and primers VL1, VHA, VHB, VHC and VHD in table 18 encompass codons AGY and RGYW, Marks et al anticipate the claims. Marks et al teach that partial randomization of VL CDR3 resulted in mutant scFvs with 16 fold higher affinity for c-erbB-2 (see column 18) and that mutating amino acids which

contact antigen has been shown to be an effective means of increasing antibody affinity (see column 17). Marks et al teach that VH CDR3 occupies the center of the binding pocket and thus, mutations in this region are likely to result in an increase in affinity. Marks et al teach VH and VL CDR3 randomization produced antibodies with increased affinity (see Example 3, columns 59-70). Marks et al teach scFv, Fab, F(ab)2, dsFvs, and diabodies (see column 2, lines 21-30 and column 19, lines 5-13 and Example 6). Marks et al teach c-erbB-2 antibodies are attached to a label, a radionuclide, a drug, a liposome, a ligand, an antibody, an antigen binding domain, or cytotoxins including *pseudomonas endotoxin A* (PE), diphtheria toxin (DT), ricin A and abrin (see columns 3, 23-26). Further, Marks et al teach nucleic acids encoding the mutated antibodies and expression cassettes (see examples 2-3, 5-6).

14. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Goyenechea et al (Proc. Natl. Acad. Sci. USA. 93:13979-13984,1996).

The claims have been described supra. Due to the indefinite nature of the claims (see 112 2nd (b) on page 3 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the parental sequence (i.e. AGY encodes a serine in the parental sequence that is substituted with glycine in the mutated sequence).

Goyenechea et al teach affinity maturation of heavy and light chain CDR1 wherein the mutations or substitutions are associated with hot spot sequence motifs comprising G/A-G-T/C-A/T (Pu-G-Py-A/T) and AGY (see page 13979) and Goyenechea

et al teach amino acid substitutions that increased antibody affinity to 2-phenyloxazolone by a factor of 10 and 8 fold (see page 13982).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yelton et al (The Journal of Immunology. 155: 1994-2004, 1995) as applied to claims 1-5, 8, 10, 21, 27, 31 above and further in view of Chowdhury et al [a] (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998) and Chowdhury et al [b] (Journal of Molecular Biology. 281: 917-928, 1998).

Claims 1-5, 8, 10, 12-14, 16, 21, 27, 31 and their interpretations have been described supra.

Claims 6, 9, 11, 15, 17-20, 28, 32-34, 36-37 and 39-40 recite that the antibody is anti-mesothelin antibody SS and can be a scFv, Fab, F(ab)2, or a dsFv (disulfide stabilized Fv) and comprises the *pseudomonas endotoxin* PE38, or PE35, or PE40. Claims 33-34, 36-37 and 39-40 recite methods of killing a malignant cell with the mutant antibodies comprising cytotoxic fragments PE35, PE38 or PE40.

Yelton et al have been described supra. Yelton et al do not specifically teach the anti-mesothelin antibody SS or cytotoxic conjugates thereof or methods of killing malignant cells using the mutated antibody-cytotoxin molecules. These deficiencies are made up for in the teachings of Chowdhury et al [a] and Chowdhury et al [b].

Chowdhury et al [a] teach anti-mesothelin antibody SS (SS scFv) conjugated to PE38 and methods of killing malignant cells with the SS scFv-PE38 immunotoxin. Chowdhury et al [a] teach anti-mesothelin antibodies that were not useful because of low affinity and poor internalization (see page 669, right column). Chowdhury et al [a]

teach phage display as an important tool for identifying high affinity clones and a scFv, a dsFv, or a Fab can be fused in-frame with the minor surface protein gIIIp of the filamentous phage (see page 670, left column). Chowdhury et al [a] teach the isolation of SS scFv, which binds with high affinity to mesothelin and the SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors (see pages 671-674). Further, Chowdhury et al [a] teach the significance of immunotoxin stability and for effective therapy the immunotoxin must be very stable at physiological temperature (see page 673, left column and Figure 4).

Chowdhury et al [b] teach the anti-mesothelin antibody SS produced in the Chowdhury laboratory is stable with $t_{1/2}$ of greater than 24 hours at 37°C (see Figure 1a and legend) and emphasize that the therapeutic success of a drug (i.e. immunotoxin) depends on its stability at 37°C and the ability to produce it in high yield (see page 918). Chowdhury et al [b] teach VH and VL mutations in the anti-mesothelin scFv K1 that significantly improved the stability and yield of the K1 scFv immunotoxins (see abstract) and the method can be used to improve other scFvs (i.e. the SS scFv). Chowdhury et al [b] teach that Fv is preferred because immunotoxins made with Fvs are smaller, which facilitates tumor penetration and Fvs are less immunogenic in humans (see page 918).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have mutated CDRs using codon-based mutagenesis to efficiently produce a cytotoxic anti-mesothelin SS antibody that rapidly penetrates tumors, has reduced immunogenicity, and has increased affinity and

specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Yelton et al and Chowdhury et al [a] and Chowdhury et al [b].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have mutated CDRs using codon-based mutagenesis to efficiently produce a cytotoxic anti-mesothelin SS antibody that rapidly penetrates tumors, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Yelton et al and Chowdhury et al [a] and Chowdhury et al [b] because Yelton et al teach codon-based mutagenesis which efficiently introduces large numbers, and potentially all combinations of amino acid substitutions into a specifically targeted CDR (see page 1995, left column) of a tumor specific antiobody and codon-based mutagenesis utilizes randomized oligonucleotides, which include A/CNN and NNG/T, where N is any nucleotide and NNG/T yields 32 codons, representing all twenty amino acids. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have mutated CDRs using codon-based mutagenesis to efficiently produce a cytotoxic anti-mesothelin SS antibody that rapidly penetrates tumors, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Yelton et al and Chowdhury et al [a] and Chowdhury et al [b] because Chowdhury et al [a] teach that the SS scFv that binds with high affinity to mesothelin and the SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas a different anti-mesothelin scFv with low affinity

was not useful for targeted therapy. Additionally, Chowdhury et al [a] and Chowdhury et al [b] teach the significance of immunotoxin stability for effective therapy and Chowdhury et al [b] teach a mutagenesis method applicable to any scFv for increasing the stability of an antibody. Therefore, it would have been obvious to produce a scFv-, a dsFv-, a Fab-, or a $F(ab)_2$- PE immunotoxin having the combination of selective cytotoxicity, high activity, and stability for use as a therapeutic agent. Thus, it would have been obvious to one skilled in the art to have mutated CDRs using codon-based mutagenesis to efficiently produce a cytotoxic anti-mesothelin SS antibody that rapidly penetrates tumors, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Yelton et al and Chowdhury et al [a] and Chowdhury et al [b].

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al (U.S. Patent 5,977,322, 6/13/1996) as applied to claims 1-5, 8, 10, 12-14, 16, 21, 27, 31 above and further in view of Chowdhury et al [a] (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998) and Chowdhury et al [b] (Journal of Molecular Biology. 281: 917-928, 1998).

The claims have been described supra. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted as being drawn to the bacteriophage expression (i.e. phage display) of the mutated antibodies. Due to

the indefinite nature of the claims (see 112 2nd (b) on pages 3-4 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the substituted/mutated sequence.

Marks et al have been described supra. Marks et al do not specifically teach the anti-mesothelin antibody SS or cytotoxic conjugates thereof or methods of killing malignant cells using the mutated anti-mesothelin antibody SS-cytotoxin molecules. These deficiencies are made up for in the teachings of Chowdhury et al [a] and Chowdhury et al [b].

Chowdhury et al [a] have been described supra.

Chowdhury et al [b] have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have randomized certain CDR residues using codon-based mutagenesis (NNS oligonucleotides) to efficiently produce a cytotoxic anti-mesothelin SS antibody that penetrates tumors easily, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Marks et al and Chowdhury et al [a] and Chowdhury et al [b].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have randomized certain CDR residues using codon-based mutagenesis (NNS oligonucleotides) to efficiently produce a cytotoxic anti-mesothelin SS antibody that penetrates tumors easily, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells

expressing mesothelin in view of Marks et al and Chowdhury et al [a] and Chowdhury et al [b] because Marks et al teach CDR randomization using NNS oligonucleotides (see column 21 and Table 18), which increased antibody affinity 5 fold and 6 fold and VL CDR3 mutations produced an antibody with 16 fold higher affinity and mutated CDR3 residues 92, 93 and 94 were found to be associated with higher affinity antibodies (see column 64, lines 61-66 and column 65, lines 22-27). Marks et al additionally teach scFv, Fab, $F(ab)_2$, dsFv, and diabodies wherein the antibodies are conjugated to cytotoxins including *pseudomonas endotoxin* (PE), diphtheria toxin (DT), ricin A and abrin for killing tumor cells and tumor regression. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have randomized certain CDR residues using codon-based mutagenesis (NNS oligonucleotides) to efficiently produce a cytotoxic anti-mesothelin SS antibody that penetrates tumors easily, has reduced immunogenicity, and has increased affinity and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Marks et al and Chowdhury et al [a] and Chowdhury et al [b] because Chowdhury et al [a] teach that the SS scFv-PE38 binds with high affinity to mesothelin and kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors, whereas a different anti-mesothelin scFv with low affinity was not useful for targeted therapy. Additionally, Chowdhury et al [a] and Chowdhury et al [b] teach the significance of immunotoxin stability for effective therapy and Chowdhury et al [b] teach a mutagenesis method applicable to any scFv for increasing the stability of an antibody. Therefore, it would have been obvious to produce a scFv-, a dsFv-, a Fab-, or a $F(ab)_2$-

PE immunotoxin having increased affinity and stability to offset the loss of affinity associated with IgG conversion to scFvs and have the combination of selective cytotoxicity, high activity, and stability for use as a therapeutic agent. Thus, it would have been obvious to one skilled in the art to have randomized certain CDR residues using codon-based mutagenesis (NNS oligonucleotides) to efficiently produce a cytotoxic anti-mesothelin SS antibody that penetrates tumors easily, has reduced immunogenicity, and has increased affinity, stability and specificity for therapeutic benefit of malignant cells expressing mesothelin in view of Marks et al and Chowdhury et al [a] and Chowdhury et al [b].

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al [a] (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998) and further in view of Goyenechea et al (Proc. Natl. Acad. Sci. USA 93: 13979-13984, November 1996) and Adams et al (Cancer Research 58: 485-490, Feb 1998) and Marks et al (U.S. Patent 5,977,322, 6/13/1996).

The claims have been described supra. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted as being drawn to the bacteriophage expression (i.e. phage display) of the mutated antibodies. Due to the indefinite nature of the claims (see 112 2nd (b) on page 3 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the parental

sequence (i.e. AGY encodes a serine in the parental sequence that is substituted with glycine in the mutated sequence).

Chowdhury et al [a] have been described supra. Chowdhury et al [a] do not teach hot spot sequence motifs, or mutating CDR hot spots for affinity maturation or that increased affinity leads to improved selective tumor delivery or disulfide-stabilized Fvs (dsFvs). These deficiencies are made up for in the teachings of Goyenechea et al and Adams et al and Reiter et al.

Goyenechea et al teach that affinity maturation of antibodies requires localized hypermutation and antigen selection and hypermutation is particularly active in heavy and light chain CDRs due to the local accumulation of hot spots, which are nucleotide sequences where mutations are frequently concentrated during the in vivo affinity maturation process. Goyenechea et al teaches the hot spot sequence motifs G/A-G-T/C-A/T (Pu-G-Py-A/T) and AGY in antibody V genes (see pages 13979, 13982 and 13983). Goyenechea et al teach that hot spots are paramount for affinity maturation and teach antibody amino acid substitutions in hot spots that increased antibody affinity by a factor of 10 and 8.(see page 13982). Goyenechea et al teach how evolution has optimized the mutability of individual residues to minimize deleterious mutations in antibody genes.

Adams et al teach that increased affinity leads to improved selective tumor delivery of scFv antibodies. Adams et al teach affinity mutants of a human scFv (C6.5) that binds to a HER2/neu epitope expressed on the surface of ovarian carcinoma cells wherein the scFvs differed from each other by only one to three amino acid residues in

the VH and VL CDR3, yet differed in affinity for the same HER2/neu by 320-fold (see page 485 and Table 1). Adams et al teach radioiodination of the scFvs and tumor retention of the highest affinity scFv was 7-fold greater than that of a mutant with 320-fold lower affinity for HER2/neu (see pages 487-488).

Marks et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Goyenechea et al and Adams et al and Marks et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scfv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Goyenechea et al and Adams et al and Marks et al because Chowdhury et al [a] teach that the SS scFv binds with high affinity to mesothelin and the SS scFv-PE38

immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas anti-mesothelin antibodies with low affinity and poor internalization (mAb K1) were not useful for targeted therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFv-PE or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Goyenechea et al and Adams et al and Marks et al because Goyenechea et al teach hot spot sequence motifs G/A-G-T/C-A/T (Pu-G-Py-A/T) and AGY in antibody V genes for antibody affinity maturation and mutations of CDR hot spot motifs produced antibody mutants with 10 and 8 fold increased affinity. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFv-PE or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Goyenechea et al and Adams et al and Marks et al because Adams et al teach that increased affinity leads to improved selective tumor

delivery of scFvs. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFV-PE or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Goyenechea et al and Adams et al and Marks et al because Marks et al teach Marks et al teach CDR randomization (see column 21 and Table 18), which increased antibody affinity and CDR3 residues 92, 93 and 94 were found to be associated with higher affinity antibodies when they were mutated (see column 64, lines 61-66 and column 65, lines 22-27). Marks et al additionally teach scFv, Fab, $F(ab)_2$, dsFv, and diabodies wherein the antibodies are conjugated to cytotoxins including *pseudomonas endotoxin* (PE), diphtheria toxin (DT), ricin A and abrin for killing tumor cells and tumor regression. Therefore, it would have been obvious to increase the affinity and stability of the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) by mutating CDR hot spots in order to selectively target the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv, diabodies) and increase the cytotoxic effect on malignant cells expressing mesothelin for therapeutic benefit. Thus, it would have been obvious to one skilled in the art to have combined the teachings of Marks et al and Goyenechea et al and only mutate CDR hot spots in the SS scFV-PE as taught by Chowdhury et al [a] because other low affinity and poorly internalized anti-mesothelin

antibodies (mAb K1) were not therapeutically useful and increased affinity leads to improved selective targeting as taught by Adams et al and only mutating CDR hot spots avoids having to screen large and multiple phage libraries and minimizes deleterious mutations and the small Fv size facilitates tumor penetration, reduces immunogenicity and increased stability could offset any loss in binding associated with converting whole immunoglobulins and Fabs into scFvs and would also enable immunotoxin delivery by continuous infusion over prolonged periods for therapeutic benefit of malignant cell expressing mesothelin in view of Goyenechea et al and Chowdhury et al [a] and Adams et al and Marks et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al [a] (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998) and further in view of Wagner et al (Nature 376: 732, 31 August 1995) and Pastan et al (U.S. 6,083,502, 102(e) date 1/12/1998) and Adams et al (Cancer Research 58: 485-490, Feb 1998).

The claims have been described supra. Due to the indefinite nature of claim 21 (see 112 2nd (a) on page 3 of this office action), claim 21 is interpreted as being drawn to the bacteriophage expression (i.e. phage display) of the mutated antibodies. Due to the indefinite nature of the claims (see 112 2nd (b) on page 3 of this office action), the claims are being interpreted to mean that the hot spot motifs are part of the parental

sequence (i.e. AGY encodes a serine in the parental sequence that is substituted for in the mutated sequence).

Chowdhury et al [a] have been described supra. Chowdhury et al [a] do not teach hot spot sequence motifs, or mutating CDR hot spots for affinity maturation or that increased affinity leads to improved selective tumor delivery or other types of anti-mesothelin antibodies such as Fab, $F(ab)_2$, or dsFvs and immunotoxins thereof other than *pseudomonas endotoxin* (PE). These deficiencies are made up for in the teachings of Wagner et al and Pastan et al.

Wagner et al teach hot spot serine codons AGY in the CDRs and TCN codons in the frameworks of human V gene segments. Wagner et al teach the consensus sequence [A/G,G, C/T,A/T] as a preferred target for mutation and most hot spots are associated with AGY serine codons. Wagner et al teach that biased serine codon usage in immunoglobulins has evolved to help the somatic hypermutation machinery target CDRs and thus, mutations are targeted to residues that could yield increased affinity and away from sites that are more likely to destroy the structural scaffolding.

Pastan et al teach the mesothelin antigen and methods for targeting and/or inhibiting growth of cells (i.e. malignant cells) bearing mesothelin (see abstract). Pastan et al teach the K1 antibody (see columns 28-32) and methods of using anti-mesothelin antibodies (Fv, dsFv, Fab, $F(ab)_2$, single-chain antibody) to target cytotoxins such as PE, DT, ricin and abrin to mesothelin expressing cells. (see columns 15-18).

Adams et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al because Chowdhury et al [a] teach that the SS scFv binds with high affinity to mesothelin and the SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas other anti-mesothelin anribodies with low affinity and poor internalization (mAb K1) were not useful for targeted therapy. Additionally, Chowdhury et al [a] teach the significance of immunotoxin stability for effective therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of

success to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al because Wagner et al teach hot spot codons AGY and TCN and the consensus sequence [A/G,G, C/T,A/T] is a preferred target for mutation and hot spot mutations are targeted to residues that could yield increased affinity and are away from sites that are more likely to destroy the structural scaffolding. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al because Pastan et al teach the mesothelin antigen and antibody (K1) methods for targeting and/or inhibiting growth of cells (i.e. malignant cells) bearing mesothelin (see abstract) with cytotoxins such as PE, DT, ricin and abrin. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (i.e.

Fab, $F(ab)_2$, dsFv) in order to avoid screening large and multiple antibody phage libraries, avoid deleterious mutations, increase antibody affinity, stability and specificity, facilitate tumor penetration and reduce antibody immunogenicity and toxicity related to poor targeting for therapeutic benefit of malignant cells expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al because Adams et al teach that increased affinity leads to improved selective tumor delivery of scFvs. Therefore, it would have been obvious to increase the affinity and stability of the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) by mutating CDR hot spots in order to selectively target the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) and increase the cytotoxic effect on malignant cells expressing mesothelin for therapeutic benefit. Thus, it would have been obvious to one skilled in the art to have combined the teachings of Pastan et al and Wagner et al and only mutate CDR hot spots in the SS scFV-PE as taught by Chowdhury et al [a] because other low affinity and poorly internalized anti-mesothelin antibodies (mAb K1) were not therapeutically useful and increased affinity leads to improved selective targeting as taught by Adams et al and only mutating CDR hot spots avoids having to screen large and multiple phage libraries and minimizes deleterious mutations and the small Fv size facilitates tumor penetration, reduces immunogenicity and increased stability could offset any loss in binding associated with converting whole immunoglobulins or Fabs into scFvs and would also enable immunotoxin delivery by continuous infusion over prolonged periods for therapeutic benefit of malignant cell expressing mesothelin in view of Chowdhury et al [a] and Wagner et al and Pastan et al and Adams et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (703) 605-1200. The examiner can normally be reached at (703) 605-1200 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER